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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,977	06/22/2006	**Stefan Johan Koppelman**	677132000200	8397

25225 7590 03/15/2012

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
03/15/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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PatentDocket@mofo.com
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Office Action Summary	Application No.	Applicant(s)	
	10/583,977	KOPPELMAN ET AL.	
	Examiner	Art Unit	
	NORA ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 November 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *21-30* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21-30* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's argument filed on 11/23/2011 is acknowledged.

2. Claims 21-22 and newly added claims 23-30 are pending and currently under consideration as they read on a method to desensitize a subject to an allergic reaction to 2S albumin comprising administering reduced and alkylated 2S albumin to the subject.

3. The following rejections are necessitated by the amendment filed on 11/23/2011.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 21-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "essentially all" in claims 21 and 26 is a relative term which renders the claims indefinite. The term "essentially all" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 25 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "reduction of any IgE response to zero" claimed in claims 25 and 30 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 11/23/2011 points to Figures 3 and 4 herein as described on page 21 of the specification at lines 1-24 for support for the newly added limitation "reduction of any IgE response to zero" as claimed in claims 25 and 30. However, the specification does not provide a clear support of "reduction of any IgE response to zero." Figures 3 and 4 do not show reduction of any IgE response to zero. Instead, they show that reduced and alkylated brazil nut 2 S allergen does not induce a reduced alkylated brazil nut 2 S allergen-specific IgE response in Brown Norway mice. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

8. Claims 25 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for : a method of orally or parenterally administering reduced

and alkylated brazil nut 2S allergens wherein the administration results in the absence of an induction of reduced and alkylated brazil nut 2S allergen-specific antibodies, does not reasonably provide enablement for : a method to desensitize a subject to an allergic reaction to 2S albumin which method comprises administering to said subject a 2S albumin which has been modified by reducing essentially all of the disulfide bonds thereof and alkylating the resultants wherein said administering is oral or parenteral **and said desensitizing results in reduction of any IgE response to zero** of claim 25; and a method to desensitize a subject to an allergic reaction to a subsequently administered 2S albumin which method comprises previously administering to said subject a modified form of said 2S albumin which has been modified by reducing essentially all of the disulfide bonds thereof and alkylating the resultants wherein said administering is oral or parenteral **and said desensitizing results in reduction of any IgE response to zero** of claim 30.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The art of Oommen et al. (PTO-892; Reference U) teaches throughout the reference that brazil nut 2S albumin Ber e 1 contains numerous linear IgE epitopes and that IgE reactivities amongst Ber e 1 allergic subjects were polymorphic (In particular, Chapter 2, Figure 5 of Chapter 2, page 119, pages 147-148, whole document). The reduction and alkylation of Ber e 1 would not effect IgE binding to linear epitopes. Therefore, the method is not enabled for a method wherein "any IgE response" goes "to zero." As taught in the reference patient responses are polymorphic and the total elimination of an IgE response is not predictable. In addition, the art shows that the method would not result in an eliminated IgE response to the linear, non-

conformational epitopes of 2s albumin. Furthermore, the claims are not limited to reduced, alkylated or native 2s albumin responses. Instead the claims recite "any IgE response" and the claims are especially not enabled for the complete reduction of an IgE response having any specificity.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 21-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/074250 (IDS filed on 08/22/2006) in view of Bartolome et al. (PTO-892 mailed on 08/17/2010; Reference U) for the same reasons as set forth in the Office Action mailed on 06/23/2011.

WO 02/074250 teaches a method for treating an individual suffering from food allergy and prevention of food allergies in non-sensitized patients comprising administering to said individual a therapeutically effective amount of an allergen modified by reduction and alkylation wherein the allergen is brazil nut 2S albumin (In particular, page 3, line 24 to page 4, line 30,

page 40, lines 1-29, Appendix 8, page 176, claims, whole document); wherein said reduction uses a reducing agent selected from the group consisting of 2-mercaptoethanol, dithiothreitol, dithioerythritol, and tributylphosphine (In particular, page 32, line 5-21); said alkylation uses an alkylating agent chosen selected from the group consisting of N-ethylmalimide, cystamine, iodoacetamide, and iodoacetic acid (In particular, page 32, lines 5-21); and results in treating, preventing and down regulation of the production of allergen specific IgE antibodies (In particular, page 3, line 24 to page 4, line 30, page 40, lines 1-29, whole document).

Bartolome et al. teaches that 2S albumin Ber e 1 major allergen of Brazil nut is a sulfur-rich allergen having 8% cysteine that forms disulfide bonds which are important for its conserved 2 S albumin structure. (In particular, page 136 right column) Ber e 1 is resistant to proteolytic digestion due to the disulfide bonds and the reference teaches that the stable structure allows the protein to reach and pass through the mucosal membrane of the intestine without complete enzymatic proteolytic degradation or acidic denaturation in the digestive tract, conferring its allergenic properties (In particular, last paragraph).

It would have been obvious to combine the specific teachings within the WO 02/074250 reference to arrive at the instantly claimed invention, particularly because Bartolome et al. teaches that the stable conformational structure of the Ber e 1 protein contributes to its allergenicity. It would have been obvious to alter the conformational structure of the Ber e 1 major allergen of Brazil nuts before administering the allergen to treat allergies to brazil nuts. WO 02/074250 specifically teaches how to alter the conformational structure of a protein due to disulfide bonds by reduction and alkylation to result in allergens, such as Ber e 1, with reduced IgE binding. It would further have been obvious that such a method would have inherently

modified all of the disulfide bonds present in the protein as the reduction and alkylation is not being targeted to specific disulfide bonds. It would also have been obvious to administer the modified protein prior to exposure in the form of a vaccine and to treat already sensitized allergic individuals. In addition, because arriving at the claimed method steps is obvious given the combination of the teachings in the references, the result of "reduction of any IgE response to zero" would have been an inherent feature of the obvious active method steps.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 11/23/2011 have been fully considered, but have not been found persuasive.

Applicant argues:

> "There is only one outstanding basis for rejection -- all claims were rejected as obvious over WO02/074250 (Panacea) in combination with Bartolome, *et al., Allergol et Immunopathol. (1997)* 25:135-144 (Bartolome). It is the position of the Office that Panacea teaches that allergens may be reduced and alkylated to disrupt one or more sulfide bonds and that Bartolom6 teaches that the 2S albumin allergens of Brazil nut are sulfur-rich allergens, and thus subject to such treatment. (The Examiner also asserts that Panacea teaches that such modified allergens induce production of T-helper-1 mediated subclasses of IgG citing page 3, line 24-page 4, line 30 and page 40, lines 1-29. Applicants are unable to find such a teaching).
>
> While the Examiner is correct that Panacea teaches reduction of disulfide bonds and subsequent alkylation as means to modify allergens, there is no teaching that essentially all of the disulfide bonds be reduced and alkylated so as to result, as required by new claims 25 and 30, that production of IgE in response to the allergen will be completely eliminated.
>
> Bartolome is cited, apparently, for its focus on Brazil nut 2S albumin of claims 22 and 27 since only peanut albumin is illustrated in Panacea. Not only does Panacea fail to focus on Brazil nut albumin, it also fails to suggest that essentially all of the disulfide bonds be reduced and

alkylated. In fact, it appears to teach away from this by stating merely that "one or more" such bonds should be reduced (see Abstract and page 3, lines 24-26). This is insufficient to suggest that essentially all of the disulfide bonds be reduced, even if that could be considered included within the genus that the Office asserts is suggested by Panacea. This was made clear by the decision in *Genetics Institute, LLC, v. Novartis Vaccines & Diagnostics, Inc.,* (Fed. Cir. 2011) 2011 U.S. App. LEXIS 17513, decided August 23,2011, where claims which required the presence of a specific region of a truncated recombinant Factor VIII were considered non-obvious over claims that included that possibility but did not require it. (The reason claims were compared was that the case involved a potential interference between two issued patents.) Clearly Panacea does not require that essentially all disulfide bonds be reduced, nor does it suggest that it would be desirable to do so.

The desirability of reducing essentially all of these disulfide bonds is verified by the data in the present application as compared to the results (albeit related to mutant peanut allergen) shown in Panacea. Figures 3 and 4 of the present application and the corresponding description on page 21 show that the method of the invention results in the complete elimination of an IgE response. That is not the case with the modified peanut allergen of Panacea as shown in Figure 57. In many patients, an IgE response was significant.

This is extremely important since the consequences of an IgE response are often catastrophic. Bartolom6 demonstrates this on page 137 at the left-hand column where symptoms of an allergic response resulted in confinement to intensive care for 24 hours. With the magnitude of such a response, it is clear that the IgE response should be completely eliminated.

Further, since neither Panacea nor Bartolome describe conversion of an immune response from a T helper 2-mediated reaction toward a T helper 1-mediated reaction as does the present specification on page 4 lines 1-5, and as needed to desensitize the subject to subsequent administration of the allergen, claims 26-30 are not obvious for this reason as well.

Withdrawal of the rejection is therefore believed proper.

Conclusion

The claims as amended require that essentially all disulfide bonds be reduced and alkylated in order to provide significant desensitization both to the allergen as administered and to subsequent administration of unaltered allergen. There is no suggestion in Panacea that essentially all disulfide bonds be reduced and alkylated; indeed the emphasis in Panacea is on mutating the IgE epitopes. Bartolom6 adds nothing to Panacea except to show that Brazil nut 2S albumin is indeed an allergen that depends at least to some extent on conformation for effectiveness. Although the Office asserts that there was no comparison of the noted remaining ability of the reduced subunits to bind IgE to that of the native albumin, it is clear from the binding of the subunits that Bartolom6 fails to teach or suggest that altering the conformation *per se* fails to effectively destroy the ability of the allergen to elicit an IgE response and indeed to desensitize the subject to future administration of the unmodified allergen so as to eliminate completely an IgE response."

The Examiner's position:

Applicant's argument:

Panacea does not focus on Brazil nut albumin

It is the Examiner's position that the WO 02/074250 and Barolome references teach that peanut allergens are other clinically important food allergens. The reduction and alkylation of peanut allergens taught in the WO 02/074250 reference works for peanut allergens for the same reasons that reduction and alkylation of 2S albumin allergens from Brazil nuts and other tree nuts works in the instant invention. As such, the WO 02/074250 reference is analogous art. It is noted that the WO 02/074250 reference is not being relied on for its teaching of 2S albumin allergens.

Applicant's argument:

Panacea teaches reduction of disulfide bonds and subsequent alkylation as means to modify allergens but does not teach that essentially all of the disulfide bonds be reduced and alkylated

A. teaches away from this by stating merely that "one or more" such bonds should be reduced (see Abstract and page 3, lines 24-26).

B. the emphasis in Panacea is on mutating the IgE epitopes

It is the Examiner's position that the reference teaches:

on page 32, lines 5-21

> "In certain embodiments, the modified allergens of the present invention may be reduced and alkylated in order to disrupt one or more disulfide bonds that are present in the natural allergen. Methods for reducing and alkylating proteins have been described in the art, e.g., for a review see Herbert et al., *Electrophoresis* 22:2046, 2001. Examples of reducing agents that may be used include but are not limited to 2-mercaptoethanol, dithiothreitol, dithioerythritol, iodoaeetamide, and tributylphosphophine. Alkylation can then be performed by blocking the SH radicals resulting from the cleavage of the disulfide bonds in a conventional manner, e.g., using iodoacetamide, iodoacetic acid, or derivatives thereof. More generally, at least one disulfide bond can be reduced and alkylated to produce cysteine residues with side chains having the chemical formula -CH2-S-[CH2]n-R' wherein n is an integer between 1 and 5 and R' is selected from the 1-5 carbon groups consisting of alkyl groups (e.g., methyl, ethyl, n-propyl, etc.); carboxy alky] groups (e.g., carboxymethyl, carboxyethyl, etc.); cyano alkyl groups (e.g., cyanomethyl, cyanoethyl, etc.); alkoxycarbonyl alkyl groups (e.g., ethoxyearbonylmethyl, ethoxycarbonylethyl, etc.); carbomoylalkyl groups (e.g., carbamoylmethyl, etc.); and alkylamine groups (e.g., methylamine, ethylamine, etc.)." ;

and

on page 29, lines 23-30

> "It is desirable to modify natural allergens to diminish binding to IgE. In some embodiments, this is achieved while retaining the ability of the allergens to activate T-cells and/or by not significantly altering or decreasing IgG binding capacity. This requires modification of one or more IgE epitopes in the natural allergen. It will be appreciated, that for natural allergens that include one or more native disulfide bonds, this may be achieved by disrupting one or more disulfide bonds of the natural allergen. Indeed, the tertiary structure of proteins is determined in part by disulfide bonds."

The method taught by the WO 02/074250 reference to disrupt "one or more" disulfide bonds using reducing agents does not include a method of selectively disrupting some disulfide bonds and not others. The method teaches disrupting one or more because any given protein may have one or it may have more than one and all the disulfide bonds in a given protein will be disrupted. Neither the WO 02/074250 reference nor the instant application teaches a method of excluding some disulfide bonds in the disruption. Both the WO 02/074250 reference and the instant application seek to disrupt the globular fold of the allergens to diminish binding of IgE at conformational IgE epitopes.

Applicant's argument:

Panacea does not teach that production of IgE in response to the allergen be completely eliminated.

A. Figures 3 and 4 of the present application and the corresponding description on page 21 show that the method of the invention results in the complete elimination of an IgE response. That is not the case with the modified peanut allergen of Panacea as shown in Figure 57. In many patients, an IgE response was significant. This is extremely important since the consequences of an IgE response are often catastrophic. Bartolome demonstrates this on page 137 at the left-hand column where symptoms of an allergic response resulted in confinement to intensive care for 24 hours. With the magnitude of such a response, it is clear that the IgE response should be completely eliminated.

B. Although the Office asserts that there was no comparison of the noted remaining ability of the reduced subunits to bind IgE to that of the native albumin, it is clear from the binding of the subunits that Bartolome fails to teach or suggest that altering the conformation *per se* fails to effectively destroy the

> ability of the allergen to elicit an IgE response and indeed to desensitize the subject to future administration of the unmodified allergen so as to eliminate completely an IgE response."

The reduction and alkylation of the WO 02/074250 reference method would not completely diminish IgE binding if the allergen binds to IgE at linear epitopes. In the same way, the instant claims do not result in a method that would reduce IgE binding at linear epitopes either. Furthermore, Applicant has mischaracterized the results of instant Figures 3 and 4. Figures 3 and 4 show that administered RA-2S albumin did not result in the development of specific IgE against RA-2S albumin in Brown Norway rats. Figures 3 and 4 do not show that IgE specific for native 2S albumin does not bind to RA-2S albumin nor that there is "elimination," "desensitization" or "reduction of any IgE response to zero" upon administration. In the instant specification naïve rats simply did not develop specific IgE antibodies in response to the modified allergen. There is no indication in the specification that the Rats treated with RA-2S albumin would exhibit decreased IgE responses to subsequently administered native 2 S albumin, so no reduction, desensitization or elimination of the response has been demonstrated. In the WO 02/074250 reference allergic serum bound to the modified allergen and that experiment was not done in the instant specification. Furthermore, even if it had been done, the results of such an experiment would have depended upon the binding of antibodies within the individual patient's serum and upon whether or not the allergen being reduced and alkylated comprised linear IgE epitopes within the allergen.

Teaching away is not established by silence within a reference. A person of ordinary skill, upon examining Bartolome, would be not be discouraged from altering the conformation to destroy IgE epitopes. Only conformational IgE epitopes are destroyed by reduction and

alkylation and one of ordinary skill in the art would expect that linear epitopes would remain even upon changing the conformation. Any reduction of conformational epitopes would result in reduced IgE binding of the protein to antibodies which recognize those epitopes.

Applicant's argument:

Neither Panacea nor Bartolome describe conversion of an immune response from a T helper 2-mediated reaction toward a T helper 1-mediated reaction as does the present specification on page 4 lines 1-5, and as needed to desensitize the subject to subsequent administration of the allergen, claims 26-30 are not obvious for this reason as well.

It is the Examiner's position that WO 02/074250 teaches:

on page 40, lines 14-17

"In general, it is believed that the inventive modified allergens will be clinically useful in treating or preventing allergic reactions associated with any natural allergen, in particular anaphylactic allergens including but not limited to food allergens, insect allergens, and rubber allergens (e.g., latex)";

on page 33, line 18 to page 34, line 4

"**Certain preferred modified allergens of the present invention are characterized by their ability to suppress a Th2-type response and/or to stimulate a Thl-type response preferentially as compared with their ability to stimulate a Th2-type response**. Thl and Th2-type responses are well-established alternative immune system responses that are characterized by the production of different collections of cytokines and/or cofactors that can be assayed for. For example, Thl-type responses are generally associated with production of cytokines such as IL-1β, IL-2, IL-12, IL- l8, IFNα, IFNγ, TNFα, etc; Th2-type responses are generally associated with the production of cytokines such as IL-4, IL-5, IL-10, etc. The extent of T-cell subset suppression or stimulation may be determined by any available means including, for example, intra-cytoplasmic cytokine determination. In preferred embodiments of the invention, **Th2 suppression is assayed, for example, by quantitation of IL-4, IL-5, and/or IL-13 in stimulated T-cell culture supernatant or assessment of T-cell intra- cytoplasmic (e.g., by protein staining or analysis of mRNA) IL-4, IL-5, and/or IL-13; Thl stimulation is assayed, for example, by quantitation of IFNα, IFNγ, IL-2, IL-12, and/or IL-18 in activated T-cell culture supernatant or assessment of intra-cytoplasmic levels of these cytokines**."; and

page 35, lines 17 to page 36, line :

"In certain preferred embodiments of the invention, the modified allergens are provided with one or more immune system adjuvants. A large number of adjuvant compounds are known; a useful compendium of many such compounds is prepared by the NIH and can be found on the world wide web at

http://www.niaid.nih.gov/daids/ vaccine/pdf/compendium.pdf (see also Allison, *Dev. Biol. Stand.* 92:3, 1998; Unkeless et al., *Annu. Rev. Immunol.* 6:251, 1998; and Phillips et al., *Vaccine* 10:151,1992). Preferred adjuvants are characterized by an ability to stimulate a Thl- type response preferentially over Th2-type response and/or to down regulate a Th2- type response. In fact, in certain preferred embodiments of the invention, adjuvants that are known to stimulate Th2-type responses are avoided. Particularly preferred adjuvants include, for example, preparations (including heat-killed samples, extracts, partially purified isolates, or any other preparation of a microorganism or macroorganism component sufficient to display adjuvant activity) of microorganisms such as *Listeria monocytogenes, Escherichia coli* or others (e.g., bacille Calmette- Guerin (BCG), Corynebacterium species, Myeobaeterium species, Rhodoeoccus In certain preferred embodiments of the invention, the modified allergens are provided with one or more immune system adjuvants. A large number of adjuvant compounds are known; a useful compendium of many such compounds is prepared by the NIH and can be found on the world wide web at http://www.niaid.nih.gov/daids/
vaccine/pdf/compendium.pdf (see also Allison, *Dev. Biol. Stand.* 92:3, 1998; Unkeless et al., *Annu. Rev. Immunol.* 6:251, 1998; and Phillips et al., *Vaccine* 10:151,1992). **Preferred adjuvants are characterized by an ability to stimulate a Thl- type response preferentially over Th2-type response and/or to down regulate a Th2- type response. In fact, in certain preferred embodiments of the invention, adjuvants that are known to stimulate Th2-type responses are avoided**. Particularly preferred adjuvants include, for example, preparations (including heat-killed samples, extracts, partially purified isolates, or any other preparation of a microorganism or macroorganism component sufficient to display adjuvant activity) of microorganisms such as *Listeria monocytogenes, Escherichia coli* or others (e.g., bacille Calmette-Guerin (BCG), Corynebacterium species, Myeobaeterium species, Rhodoeoccus

As such, the rejection is maintained.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937.

The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 10, 2012

/Nora M Rooney/

Primary Examiner, Art Unit 1644